Elsevier Editorial System(tm) for Atherosclerosis

Manuscript Draft

Manuscript Number: ATH-D-17-01363R1

Title: Effects of vitamin D supplementation on adherence and persistence with long-term statin therapy: secondary analysis from the randomized, double-blind, placebo-controlled ViDA study

Article Type: Research paper

Section/Category: Clinical and scientific debates on atherosclerosis

Keywords: Vitamin D; statin; adherence; persistence; prescription.

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Abstract: Background and aims: Long-term statin use increases survival. However, the adherence and persistence with statin use is challenging and this influences the success of statin treatment. Our aim was to explore if monthly vitamin D supplementation (100,000-IU) improves the adherence to, and persistence with, long-term statin use in older adults.

Methods: A secondary analysis of a trial comparing data on dispensed statin prescriptions, between participants allocated to vitamin D supplementation or placebo, for those taking statin therapy. Primary outcomes were defined as adherence (proportion of days covered by prescriptions ≥80%) and persistence (non-discontinuation of the statin therapy following an allowed 30 days gap between refills) with all statins over a 24-month measurement period of statin therapy. Secondary outcomes were defined as adherence and persistence at other measurement periods for all types of statins and for individual statins.

Results: Overall, 2494 participants were on long-term statins at follow-up (vitamin D=1243, placebo=1251). Compared with placebo, monthly vitamin D supplementation did not improve the proportion with adherence (risk ratio: 1.01, p=0.62), but improved the persistence probability of taking all statins after 24 months (hazard ratio: 1.15, p=0.02). In further analyses, significant differences were observed in the adherence to simvastatin, the first-line statin therapy.

Conclusions: Monthly vitamin D supplementation improved persistence with taking statins over a 24-month measurement period in older adults on long-term statin therapy, especially for participants on simvastatin. The role of vitamin D supplementation as an adjunct therapy for patients on long-term statins merits further investigation.

Highlights

- Long-term use of statins lowers cholesterol and prevents cardiovascular disease
- Adherence to taking statins is compromised by adverse-effects such as myalgia
- Adherence and persistence to takin statins was assessed in a vitamin D trial
- Monthly vitamin D3 supplementation improved persistence in taking statins

Title: Effects of vitamin D supplementation on adherence and persistence with long-term statin therapy: secondary analysis from the randomized, double-blind, placebo-controlled ViDA study

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The number of text pages of the entire manuscript: 36;
The number of figures: 2;
The number of tables: 3;
Supplementary figures: 3;
Supplementary tables: 1.

Trial Registration clinicaltrials.gov Identifier: ACTRN12611000402943

Abstract

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Introduction

Meta-analyses of clinical trials indicate that long-term statin utilization (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) safely and significantly reduces the risk of ischemic heart disease, stroke, and all-cause mortality [1-3]. Based on the latest cholesterol guidelines of AHA-ACC (American Heart Association and the American College of Cardiology), nearly 50% of Americans aged 40-75 years are eligible for statin therapy [4]. However, observational studies demonstrate significant challenges with both long-term adherence (proportion of days covered (PDC) by prescriptions ≥80%) and persistence (non-discontinuation of the statin therapy with a specified gap between refills) with taking statin therapy. For example, one-year adherence to statins ranges from 33% to 85% [5-7], which probably influences the effectiveness of statins in disease prevention [8-10]. Therefore, improving adherence to and persistence with taking statins has a potential clinical benefit for millions of patients.

Adherence and persistence with taking medications, in general, can be influenced by barriers acting at a number of levels. These barriers include those in the individual patient (e.g. side effects, forgetfulness), the physician (e.g. not following guidelines, poor physician-patient communication), and the health care system (e.g. cost, insurance status) [11]. One of the principal reasons for non-adherence and discontinuing of statins is pain-related adverse effects [12], particularly myalgia [13]. Although the pathophysiology of statin-related pains remains unclear, several observational studies have linked the problem with vitamin D deficiency [14-16], and one single group interventional study reported that vitamin D supplementation reverses statin intolerance caused by pain-related adverse effects [17]. The latter finding is supported by a meta-analysis of randomized controlled trials showing that vitamin D supplementation reduces pain levels in patients with chronic pain (not on statin therapy) [18]. Overall, the above research suggests that vitamin D supplementation might be an effective adjunct to improve the adherence and persistence with long-term statin therapy.

To our knowledge, no randomized controlled trials have explored whether vitamin D supplementation can improve the adherence and persistence with taking statins. To address this issue, all participants on long-term statin therapy in a population-based trial of vitamin D supplementation were selected to assess the effects of vitamin D supplementation on long-term adherence and persistence with taking statins.

Patients and methods

Participants

This study is a secondary analysis of participants on long-term statin therapy at follow-up evaluation of the Vitamin D Assessment (ViDA) study, a population-based, randomized, double-blind, placebo-controlled trial to evaluate the effects of monthly vitamin D supplementation on cardiovascular disease and other health outcomes. Ethics approval was given by the New Zealand Multi-region Ethics Committee in Wellington in October 2010 (MEC/09/08/082/AM). Briefly, 5110 Auckland adults, aged 50-84 years, were recruited and randomized to taking monthly cholecalciferol (100,000-IU) or placebo, in identical oral capsules, for up to 4 years (2011-2015). Full details of the study design have been published, including the requirement of written informed consent to participate [19]. Participants of the current sub-study were included if, after randomization, they had two or more prescription of statins, and had ≥90 days of statin treatment.

Data collection

Demographic data of eligible participants were collected at the baseline interview between 2011 and 2012 [19]. This also included measurement, in light clothing without shoes, of height to the nearest 0.1 cm, and weight to the nearest 0.1 kg, from which body mass index (BMI) was calculated (kg/m^2). As well, a non-fasting blood sample was collected and stored at −80°C for later measurement of serum total cholesterol and high-density lipoprotein cholesterol levels by an Advia 2400 analyzer (Siemens Healthcare Diagnostics), and 25-hydroxyvitamin D (25(OH)D) by liquid chromatography–tandem mass spectrometry (ABSciex API 4000) in a local laboratory participating in the Vitamin D External Quality Assessment Scheme program (www.deqas.org). Season-adjusted (deseasonalized) 25(OH)D values were estimated for each participant from a sinusoidal model with parameters derived from baseline 25(OH)D values from all participants in the main ViDA study [20].

Randomization

Participants were randomized if they returned this questionnaire within four weeks, confirmed they took the study capsule, and their blood serum calcium concentration was ≤2.50 mmol/L. The randomization list was generated by a statistician who was not involved in outcome measures, by strata of 5-year age groups and ethnic categories, within randomly assigned blocks of 8, 10, or 12. The randomization process was done automatically, all the investigators and participants were blinded until the end of study.

Intervention

Vitamin D_3 (100,000-IU or 2.5mg) or placebo soft-gel oral capsules (Tishcon Corporation, Westbury, New York, USA) were mailed to participants' homes. Two capsules were sent in the first mail after randomization (i.e., 200,000-IU bolus or placebo), followed by a 2.5-mg (100,000-IU) capsule of vitaminD_3 (or placebo) taken monthly thereafter. Information on study capsule adherence (vitamin D_3 or placebo) was collected by questionnaires, which were mailed with capsules to participants' homes every month (or every 4-month after November 2013) along with a pre-addressed return pre-paid envelope. Mean 25(OH)D levels at 6, 12, 24, and 36 months after randomization were measured in a randomly selected sample of 441 participants (of 515 invited) who returned regularly for blood sample collection (220 participants were included in this secondary analysis).

Prescription data of participants were identified by linking each person's unique National Health Index (NHI) number with the Pharmaceutical Claims Data Mart (Pharms DM), which includes all subsidized prescriptions in New Zealand, and are collected by both the Ministry of Health (MOH) and Pharmaceutical Management Agency (www.health.govt.nz). All prescriptions for statins were extracted by Anatomical Therapeutic Chemical Classification System (ATC) code (C10A and C10B) from 6 months before randomization to the end of the study follow-up (31 July 2015). For each statin

prescription, the chemical name, date of dispensing, quantity dispensed, daily dose and frequency, and days of supply, were used for calculating the adherence and persistence with taking statins.

Outcomes

All study outcomes were specified before data analysis. Adherence of statin was measured by the PDC, which is the preferred method of measuring medication adherence, as recommended by The Pharmacy Quality Alliance (PQA) [21]. PDC is calculated as the total days of supply divided by a specified fixed measurement period [22]. The threshold of adherence is a PDC ≥80%. Statin persistence was defined as non-discontinuation of the statin therapy, allowing for a specified gap between refills, which was selected in this study to be 30 days [23]. The measurement period of this study began on the index date (the first day with statin therapy after the date of randomization) and extended for a subsequent fixed period (e.g. 6-, 12-, 24-month) or until death, and the baseline measurement period was defined as 6 months before randomization. The related definitions were illustrated in **Supplementary Figure 1**.

The primary outcomes were adherence and persistence with taking all types of statins for a 24-month measurement period after the index date. The secondary outcomes were adherence and persistence with taking all statins for 6- and 12-month measurement periods, and individual statins for 6-, 12- and 24-months after the index date. Four categories of statins or statin combination are subsidized in New Zealand, namely simvastatin, atorvastatin, pravastatin, and ezetimibe with simvastatin. In the analysis of adherence and persistence with taking all statins, the four statin categories were considered as a single class of prescriptions in the analysis.

Statistical analysis

The t-test or chi-square test were used to examine differences in baseline characteristics between the vitamin D and placebo groups. Risk ratios (RR) and corresponding two-sided 95%CI were estimated

with Cochran–Mantel–Haenszel chi-square for cumulative adherence to taking statins (PDC ≥80% for each time period) at the 6-, 12- and 24-month time points. The Cox proportional hazards model was used to investigate any differences in survival (persistence) probability between the two groups (hazard ratio (HR)), along with Kaplan-Meier curves of survival (persistence with taking statin). Missing data on the number of days of taking statins were estimated by dispensed quantity, daily dose and refilled interval. Also, atorvastatin daily dose equivalent and total amount of atorvastatin dose equivalent during the follow-up were calculated in the sensitivity analyses [24]. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and two-sided $p \leq 0.05$ was considered statistically significant. We opted not to correct p values for our two primary outcomes, based on the arguments of Rothman [25].

Results

Study Participants

The selection of participants in this sub-study, from all 5110 participants randomized into the main trial (collected from 2011-2012, followed up to July 2015) is shown in **Figure 1**. Briefly, 2648 participants were excluded for following reasons: two participants withdrew complete consent, one withdrew consent to analyze pharmaceutical data, 2501 had no statin prescription, 100 had only one statin prescription and 12 had less than 90 days of statin treatment. Of the 2494 selected participants, 1243 were in the vitamin D group and 1251 in the placebo group.

There were no significant differences between the vitamin D and placebo groups in the participant characteristics at baseline (**Table 1**). There were approximately equal numbers of men and women, and similar mean age of 67 years. More than 75% of participants had been told by a doctor (question in baseline interview) they had high cholesterol. The deseasonalized 25(OH)D (25-hydroxyvitamin D) concentration was similar between two groups, with overall average of 64.9 nmol/L (SD 22.4).

Of 441 randomly selected participants were agreed to return at 6, 12, 24, and 36 months after randomization for collection of blood samples to measure 25(OH)D levels, 220 included in this secondary analysis. Observed serum 25(OH)D levels during follow-up were given in **Supplementary Table**, and much higher (by > 45.0 nmol/L) in the vitamin D group compared with placebo, with mean (SD) 25(OH)D respectively, being: 123 (36) nmol/L and 72 (31) nmol/L at 6 months; 109 (36) nmol/L and 59 (28) nmol/L at 12 months; 129 (38) nmol/L and 62 (25) nmol/L at 24 months; and 133 (41) nmol/L and 61 (29) nmol/L at 36 months.

Statin use in the baseline period

There were 2099 (84%) participants prescribed any types of statin therapy at any time during the baseline measurement period (the 6 months before randomization). During this period, 1257 participants were prescribed simvastatin, 948 atorvastatin, 9 pravastatin and 15 ezetimibe with simvastatin. Furthermore, among the statin users, most received simvastatin only (n=1130) or atorvastatin only (n=823). The proportion of statin users during the baseline measurement period was similar between two groups (**Table 1**).

During the baseline measurement period (6 months before randomization), some participants (15.8%) selected for this analysis were not on prescribed statins because they started after randomization. Regardless, adherence during the 6 months prior to randomization to taking all statins and individual statins was similar between vitamin D and placebo groups (all statins: 84.2 vs. 83.7%, p=0.76; simvastatin: 77.1 vs. 77.2%, p=0.96; atorvastatin: 86.3 vs. 86.3%, p=0.97; **Table 2**). Furthermore, the persistence (survival) probability of taking all statins and individual statins also was similar between two groups based on the results of log-rank test (all statins: log-rank p=0.38, simvastatin: log-rank p=0.37, atorvastatin: log-rank p=0.53, **Table 3**, **Figure 2**, and **Supplementary Figures 2-3**). Adherence for pravastatin and ezetimibe with simvastatin was not calculated due to the small number of prescriptions. In addition, no significant difference was found during the baseline period in the average atorvastatin daily dose equivalent between vitamin D (22.5 mg) and placebo (21.9 mg) groups (p=0.49).

Statin use in the follow-up period

During the follow-up period after randomization (up to July of 2015), there were 2494 participants with two or more statin prescriptions, for at least 90 days of statin therapy. The median follow-up time of these participants was 3.3 years (range, 2.5-4.2), and most participants (78%) received more than two years' treatment of statins. Out of all of those prescribed statins, 1219 subjects received simvastatin therapy, 1613 atorvastatin, 100 pravastatin, and 17 ezetimibe with simvastatin. Most statin users were dispensed one category of statin during 24 months follow-up period after index date

(86.7%, n=2162), with the remainder dispensed two or more categories of statins (13.3%, n=332). The number of participants dispensed individual statins was more than for all statins combined (**Tables 2-3**) because 13.3% were prescribed more than one category of statin. There was no difference during 24 months follow-up in the proportion who reported changing statins (taking two or more categories of statin) between the vitamin D and placebo groups (12.4%, and 14.1%, respectively; p=0.22).

The detailed results for the adherence to taking all statins and individual statins during the follow-up period are reported in **Table 2**. There was no difference between the vitamin D and placebo groups in adherence to taking all types of statins over the 24-month period (after statin index date) (RR 1.01; 95%CI: 0.97, 1.05; p=0.62). A similar result was seen in vitamin D-deficient participants (<50 nmol/l) (n=670; RR 1.00; 95%CI: 0.91, 1.08; p=0.92) and in those taking a high atorvastatin daily dose equivalent (≥ 40 mg) participants (n=518; RR=1.01; 95%CI: 0.94, 1.09; p=0.74). However, for simvastatin, the first-line statin, adherence was significantly higher in the vitamin D group compared to placebo for all measurement periods: 6-month (RR 1.10; 95%CI 1.03, 1.17; p<0.01), 12-month (RR 1.09; 95%CI 1.00, 1.16; p=0.05), and 24-month (RR 1.09; 95%CI 1.00, 1.19; p=0.04). Other secondary outcomes for statin adherence were non-significant. In addition, no significant difference was found in the average atorvastatin daily dose equivalent between two groups over the 24-month period after statin index date (vitamin D group 23.7 (19.2) mg vs. placebo 23.1 (17.7) mg, p=0.12). Neither was there a difference in the total amount of atorvastatin dose equivalent (atorvastatin daily dose equivalent × days of supply) in the vitamin D group (mean 14,906 mg, SD 13,123) compared to the placebo group (mean 14,247 mg, SD 13,123) over a 24-month follow-up (p=0.19).

The persistence (survival probability) of continuing to take all types of statins (combined), and individual statins, at the end of the 6-, 12-, and 24-month measurement periods, for vitamin D treatment and placebo groups, are reported in **Table 3**, **Figure 2**, **and Supplementary Figures 2-3**. Vitamin D supplementation significantly improved the persistence with taking all statins up to the end of the 24-month measurement period after the statin index date (a primary outcome), compared with placebo (HR 1.15; 95%CI 1.02, 1.30; p=0.02). Findings were consistent, though not statistically

significant in vitamin D-deficient participants (n=670, HR 1.12; 95%CI 0.89, 1.41; p=0.34) and in high atorvastatin daily dose equivalent (≥ 40 mg) participants (n=518, HR 1.17; 95%CI 0.87, 1.57; p=0.29). For individual statin categories, persistence was lower compared to all statins combined because some participants changed their type of statin during follow up, thereby increase the probability of persistence failure. However, this applied equally to both groups and the results show that vitamin D supplementation significantly increased the persistence with simvastatin being taken at the end of 6 month (HR 1.38; 95%CI 1.09, 1.75; p<0.01), and 12 months (HR 1.20; 95%CI 1.00, 1.44; p=0.05); the finding was of borderline significant at 24 months (HR 1.15; 95%CI 0.98, 1.34; p=0.08). Other secondary outcomes for statin persistence were non-significant (**Table 3**).

Discussion

In this secondary analysis from the randomized, double-blind, placebo-controlled ViDA study, we found that monthly vitamin D supplementation significantly improved the persistence with taking statin therapy for a 24-month measurement period, compared to placebo. We also found significant improvement in the persistence with taking simvastatin for a 6-month and a 12-month measurement period, as well as adherence to taking simvastatin for 6-, 12-, and 24-month periods.

The most common reason for discontinuing cardiovascular medications is having adverse effects [12], which affected as many as 72% of patients in one New Zealand study [26]. Given the evidence linking vitamin D deficiency with statin myalgia [14-17], it is possible that vitamin D supplementation may increase persistence in taking statins by decreasing or preventing pain related side-effects.

Previous studies aiming to increase adherence and persistence with taking lipid lowering medication mainly have used behavioral intervention approaches, such as simplification of drug regimens, education, intensified patient care, pharmacy-led strategies and administrative improvements [27]. These studies show that the improvement from these interventions in adherence to taking cardiovascular medications varies widely. Specifically, the adherence improvement from simplification of the drug regimen ranges from 5% to 35% [26, 28, 29], education improvement from 4% to 8% [30-32], intensified patient care improvement from 2% to 24% [27], compared with control group. Compared with the previous research, our study shows that the absolute improvement in adherence and persistence with taking statins is of comparable magnitude.

The absolute increase in statin persistence from vitamin D supplementation over 24 months in our study was +4.4%, indicating that 23 patients on statins would need to take vitamin D supplements for 2 years to prevent 1 person stopping their statin medication. Over a longer period, which is the situation for most patients prescribed statins, the number needed-to-treat with vitamin D would be

expected to decrease, as **Figure 2** shows that the experience of the vitamin D and placebo groups are continuing to diverge. By improving the statin adherence and persistence, vitamin D supplementation may provide an effective and inexpensive way to improve the effectiveness of statin therapy in the general population.

Our study has a number of strengths. The results were based on a large, population-based, double-blind, placebo-controlled trial and are likely to apply to patients treated in the general practice setting, the baseline characteristics were comparable between vitamin D and placebo groups, including the adherence to and persistence with taking statin at baseline (6 months prior to randomization). Other strengths include: the inclusion of participants on long-term statin utilization (≥90 days) - participants who may be the most likely to benefit from statin treatment of primary and secondary prevention; our use of objective electronic records to measure statin adherence; the high compliance (84%) of taking the study capsules during the study period [20]; and the high vitamin D dose which doubled vitamin D levels in the intervention group [20]. In addition, primary and secondary outcomes of this study were all defined before the data analysis.

Our study also had several potential limitations. First, the analysis is based on information from a pharmaceutical database, which has details on dispensed prescriptions but we cannot be certain if participants took the statin medication dispensed to them. Second, adherence to statin therapy and persistence with statin taking were not specified outcomes in the study protocol, although these outcomes were defined before all of the reported analyses. Third, it is possible that participants included in our analysis did not include those who may have started taking statins in the past but stopped before entry into the study because of side effects (including myalgia). Thus, the analysis may have only included those people who tolerated statins. Fourth, this study had enough power for detecting adherence and persistence (post hoc: 87% power to detect a difference of 5% between two groups, assuming 60% of two-years adherence and persistence rates) of all statins between two groups, but it was under powered for atorvastatin (post hoc: 28% power to detect a difference of 2% between two groups, assuming 60% of two-years adherence and persistence rates) outcome

individually. Therefore, studies with larger sample size will be needed to validate the effects of vitamin D effectiveness on adherence and persistence with individual statins.

In conclusion, among adults on long-term statin therapy, monthly vitamin D supplementation, when compared with placebo, resulted in improved persistence in taking statins over two years, especially for these participants with simvastatin therapy. Furthermore, the benefits of vitamin D supplementation on the adherence to simvastatin, as the first-line statin used in New Zealand, were statistically significant for these participants on long-term simvastatin treatment. Together, these findings suggest that vitamin D supplementation could improve the adherence and persistence with taking statins in the general population. The role of vitamin D supplementation as an adjunct therapy for patients on long-term statins merits further investigation.

Conflict of interest

All authors state they have no relationship relevant to the contents of this paper.

Financial support

This work was supported by the Health Research Council of New Zealand (grant 10/400), the main government funder of research, and by the Accident Compensation Corporation of New Zealand, the main government insurer for accidents.

Author contributions

- Acquisition, analysis, or interpretation of data: Wu, Camargo, Khaw, Waayer, Lawes, Toop, and Scragg.
- Drafting of the manuscript: Wu and Scragg.
- Critical revision of the manuscript for important intellectual content: Wu, Camargo, Khaw, Waayer, Lawes, Toop, and Scragg.
- Statistical analysis: Wu and Scragg.
- Obtained funding: Scragg, Camargo, Lawes, Toop and Khaw.
- Administrative, technical, or material support: Scragg, Lawes and Khaw.
- Study supervision: Scragg.

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Table 1 Baseline characteristics of randomized participants with long-term statin therapy

Variables	Vitamin D (n=1243)	Placebo (n=1251)	*p* value
Baseline assessment			
Age (y), mean (SD)	67.3 (8.1)	67.6 (7.9)	0.40
Age (y), n (%)			0.49
50-59	221 (17.8)	194 (15.5)	
60-69	511 (41.1)	530 (42.4)	
70-79	418 (33.6)	435 (34.8)	
80-84	93 (7.5)	92 (7.3)	
Sex, n (%)			0.61
Male	821 (66.0)	814 (65.1)	
Female	422 (34.0)	437 (34.9)	
Ethnicity, n (%)			0.83
European/Other	991 (79.7)	1015 (81.1)	
Mäori	71 (5.7)	68 (5.5)	
Pacific	104 (8.4)	99 (7.9)	
South Asian	77 (6.2)	69 (5.5)	
BMI (Kg/m^2) [a], mean (SD)	29.3 (5.2)	29.5 (5.2)	0.27
BMI (Kg/m^2) [a], n (%)			0.70
<25	211 (17.1)	200 (16.0)	
25.0-29.9	563 (45.5)	563 (45.2)	
≥30.0	462 (37.4)	483 (38.8)	
Missing	7	5	
25-hydroxyvitamin D (nmol/l), mean (SD)	65.5 (22.6)	64.3 (22.1)	0.16
25-hydroxyvitamin D (nmol/l), n (%)			0.24
0-24.9	23 (1.8)	18 (1.4)	
25.0-49.9	295 (23.8)	334 (26.7)	
50.0-74.9	552 (44.4)	518 (41.5)	
75.0-99.9	372 (30.0)	380 (30.4)	

Missing	1	1	
Cholesterol level, mean (SD)			
Total cholesterol (mmol/l)	4.4 (1.1)	4.5 (1.1)	0.62
HDL-C (mmol/l)	1.3 (0.4)	1.3 (0.4)	0.95
Total cholesterol /HDL-C ratio	3.5 (0.9)	3.6 (0.9)	0.78
Missing	6	9	
High cholesterol (self-reported), n (%)			0.33
Yes	926 (75.4)	955 (77.1)	
No	302 (24.6)	284 (22.9)	
Missing	15	12	
Prescription data on statins [b]			
All statin use, n (%)	1243	1251	0.45
Yes	1053 (84.7)	1046 (83.6)	
No	190 (15.3)	205 (16.4)	
Simvastatin use, n (%)			0.84
Yes	629 (50.6)	628 (50.2)	
No	614 (49.4)	623 (49.8)	
Atorvastatin use, n (%)			0.54
Yes	480 (38.6)	468 (37.4)	
No	763 (61.4)	783 (62.6)	
Pravastatin use, n (%)			0.51 [c]
Yes	3 (0.2)	6 (0.5)	
No	1240 (99.8)	1245 (99.5)	
Ezetimibe with simvastatin use, n (%)			0.07
Yes	11 (0.9)	4 (0.3)	
No	1232 (99.1)	1247 (99.7)	

Missing data were excluded before testing group differences; n, number of participants; SD, standard deviation; HDL-C: high-density lipoprotein cholesterol; a. calculated as weight in kilograms divided by height in meters squared; b. all prescriptions at baseline measurement period (the 6 months before randomization); c. Fisher's exact test was used.

Table 2 Comparison of adherence to taking statins (proportion of days covered by prescriptions ≥ 80%) between vitamin D and placebo groups.

Outcomes	Measurement period	Adherence	Vitamin D	Placebo	Adherence Risk Ratios (95%CI), *p*
All statins	Baseline [a]	No. of participants	1053	1046	
		No	166 (15.8)	170 (16.3)	1.00
		Yes	887 (84.2)	876 (83.7)	1.01 (0.97, 1.04), *p*=0.76
	6-month	No. of participants	1243	1251	
		No	187 (15.0)	220 (17.6)	1.00
		Yes	1056 (85.0)	1031 (82.4)	1.03 (1.00, 1.07), *p*=0.09
	12-month	No. of participants	1243	1251	
		No	248 (20.0)	263 (21.0)	1.00
		Yes	995 (80.0)	988 (79.0)	1.01 (0.97, 1.05), *p*=0.51
	24-month	No. of participants	1243	1251	
		No	265 (21.3)	277 (22.1)	1.00
		Yes	978 (78.7)	974 (77.9)	1.01 (0.97, 1.05), *p*=0.62
Simvastatin	Baseline [a]	No. of participants	629	628	
		No	144 (22.9)	143 (22.8)	1.00
		Yes	485 (77.1)	485 (77.2)	1.00 (0.94, 1.06), *p*=0.96
	6-month	No. of participants	596	623	
		No	115 (19.3)	166 (26.6)	1.00
		Yes	481 (80.7)	457 (73.4)	1.10 (1.03, 1.17), *p*<0.01
	12-month	No. of participants	596	623	
		No	167 (28.0)	207 (33.2)	1.00
		Yes	429 (72.0)	416 (66.8)	1.08 (1.00, 1.16), *p*=0.05
	24-month	No. of participants	596	623	
		No	200 (33.6)	244 (39.2)	1.00
		Yes	396 (66.4)	379 (60.8)	1.09 (1.00,1.19), *p*=0.04
Atorvastatin	Baseline [a]	No. of participants	480	468	
		No	66 (13.7)	64 (13.7)	1.00
		Yes	414 (86.3)	404 (86.3)	1.00 (0.95, 1.05), *p*=0.97
	6-month	No. of participants	802	811	

		No	123 (15.3)	131 (16.2)	1.00
		Yes	679 (84.7)	680 (83.8)	1.01 (0.97, 1.05), p=0.65
	12-month	No. of participants	802	811	
		No	170 (21.2)	170 (21.0)	1.00
		Yes	632 (78.8)	641 (79.0)	1.00 (0.95, 1.05), p=0.91
	24-month	No. of participants	802	811	
		No	202 (25.2)	195 (24.0)	1.00
		Yes	600 (74.3)	616 (76.0)	0.99 (0.93, 1.04), p=0.59

a. the adherence calculation in the baseline measurement (the 6 months before randomization) only for participants on statin therapy; follow-up measurement period, begins on the first day with statin therapy after the date of randomization and extends through a fixed period; all types of statins included simvastatin, atorvastatin, pravastatin and ezetimibe with simvastatin; CI, confident intervals.

Table 3 Comparison of persistence in taking statins (allowing for 30 days grace period between prescriptions) between vitamin D and placebo groups.

Outcomes	Measurement period	Persistence	Vitamin D	Placebo	Persistence Hazard Ratio (95%CI), *p*
All statins	Baseline [a]	No. of participants	1053	1046	
		No	179 (17.0)	162 (15.5)	1.00
		Yes	874 (83.0)	884 (84.5)	0.91 (0.74, 1.23), p=0.38
	6-month	No. of participants	1243	1251	
		No	199 (16.0)	225 (18.0)	1.00
		Yes	1044 (84.0)	1026 (82.0)	1.15 (0.95, 1.39), p=0.16
	12-month	No. of participants	1243	1251	
		No	347 (27.9)	392 (31.3)	1.00
		Yes	896 (72.1)	858 (68.7)	1.15 (1.00, 1.33), p=0.05
	24-month	No. of participants	1243	1251	
		No	493 (39.7)	552 (44.1)	1.00
		Yes	750 (60.3)	699 (55.9)	1.15 (1.02, 1.30), p=0.02
Simvastatin	Baseline [a]	No. of participants	629	628	
		No	150 (23.8)	136 (21.7)	1.00
		Yes	479 (76.2)	492 (78.3)	0.90 (0.71, 1.14), p=0.37
	6-month	No. of participants	596	623	
		No	117 (19.6)	163 (26.2)	1.00
		Yes	479 (80.4)	460 (73.8)	1.38 (1.09, 1.75), p<0.01
	12-month	No. of participants	596	623	
		No	214 (35.9)	254 (40.8)	1.00
		Yes	382 (64.1)	369 (59.2)	1.20 (1.00, 1.44), p=0.05
	24-month	No. of participants	596	623	
		No	294 (49.3)	333 (53.4)	1.00
		Yes	302 (50.7)	290 (46.6)	1.15 (0.98, 1.34), p=0.08
Atorvastatin	Baseline [a]	No. of participants	480	468	
		No	71 (14.8)	62 (13.3)	1.00
		Yes	409 (85.2)	406 (86.7)	0.90 (0.64, 1.26), p=0.53
	6-month	No. of participants	802	811	

		No	146 (18.2)	154 (19.0)	1.00
		Yes	656 (81.8)	657 (81.0)	1.07 (0.85, 1.34), p=0.59
	12-month	No. of participants	802	811	
		No	253 (31.5)	286 (35.3)	1.00
		Yes	549 (68.5)	525 (64.7)	1.15 (0.97, 1.36), p=0.11
	24-month	No. of participants	802	811	
		No	387 (48.1)	421 (51.9)	1.00
		Yes	415 (51.8)	390 (48.1)	1.13 (0.98, 1.30), p=0.08

a. the persistence calculation in the baseline measurement (the 6 months before randomization) only for participants on statin therapy; follow-up measurement period: begins on the first day with statin therapy after the date of randomization and extends through a fixed period; all types of statins included simvastatin, atorvastatin, pravastatin and ezetimibe with simvastatin; CI, confident intervals.

Figure legends

Figure 1 CONSORT diagram for participants of this study.

Figure 2 Kaplan-Meier plot of persistence with all statins during baseline and 24-month measurement period (after index date).

Results of log-rank test are listed in the top right corner of each figure, number of participants at risk are shown on the bottom of each figure; persistence is defined as non-discontinuation of statin therapy within a 30 day gap between refills.

Response to reviewers

Reviewers' comments:

Reviewer #1:

This report used data from the Vitamin D Assessment (ViDA) study to examine the effect of vitamin D supplementation on adherence & persistence of statin use. Adherence was defined as the proportion of days covered >80% and persistence was defined as non-discontinuation of statin therapy over 24 months of statin therapy. This was a population-based study in which subjects received 100T units of vitamin D3 or placebo monthly. Subjects in this study who received 2 or more statin prescriptions and used them for >90 days were included. Seasonal variation in Vitamin D levels was estimated. Vitamin D levels were measured in a subset of subjects at 6, 18, 24, and 35 months. This resulted in a sample size of 1243 subjects on statins in the Vitamin D arm and 1251 on statins in the placebo arm. A large number of subjects (2601) were not included because they received less than 2 statin prescriptions.

Persistence of statin therapy increased 4.4% over 24 months with Vitamin D supplementation. Adherence was better with vitamin D for subjects taking simvastatin but not different overall and not different for atorvastatin, the second most popular statin.

1. This is an interesting contribution given the possibility that vitamin D may alter statin myalgia. A potential problem is the absence of any comparison of statin doses between the two groups. One assumes that randomization would cure this but data beat assumptions. The authors are encouraged to calculate something like an "atorvastatin dose equivalent" unit and compare statin doses between the two groups.

RESPONSE: Thank you for your suggestion. The results of "atorvastatin daily dose equivalent" between two groups have been added. There were no significant differences during the 6 months before randomization in the average atorvastatin daily dose equivalent between vitamin D (22.5 mg) and placebo (21.9 mg) groups (p=0.49) (Results Page 10), nor during the 24-month period after statin index date (vitamin D group 23.7 (19.2) mg vs. placebo 23.1 (17.7) mg, p=0.12) (Results Page 11).

2. There are multiple areas where the terms will not be crystal clear to clinicians not experienced in adherence literature. These are delineated below.
   In the abstract and elsewhere, adherence is defined as >80% days covered. This may be unclear to clinicians, as it was to this reviewer, because what covered means is unclear. Please clarify this term.

RESPONSE: We agree with you, and have reworded the definition of adherence to "proportion of days covered by prescriptions ≥80%" (Abstract Page 2, Introduction Page 3 and Table 2 Page 24).

3. The abstract and elsewhere also refer to an "allowed gap" between refills. What was the length allowed? It would be just as easy to say "allowed 30 day gap" and satisfy curiosity early.

RESPONSE: We have revised the text to state to specifically state a 30 day gap for persistence (Abstract Page 2 & Figure 2 Page 28)

4. In the introduction, the statement: "The latter finding is supported by a meta-analysis of randomized controlled trials showing that vitamin D supplementation reduces pain levels in patients with chronic pain" should specify that this is in patients not on statin therapy.

RESPONSE: We have revised the text as +suggested (Introduction Page 3).

5. Subjects were included if they had 2 or more statin prescriptions and more than 90 days of treatment. The discussion section addressing limitations should specify how this might affect the results. For example, the NLA (National Lipid Association) scoring system suggests that early onset of symptoms during statin therapy is most consistent with statin myalgia. Therefore, these criteria would miss people who stopped statins early because of discomfort.

   The authors also need to discuss that they are studying people who have tolerated statins because many are on them at baseline. It seems that those folks who are not on statins at baseline could have stopped them before starting in the study. These two comments simply mean that Vitamin D might be more or less useful if used from the start of statin treatment.

RESPONSE: Thank you for your comments. As stated in the introduction (Page 3), long-term statin utilization safely and significantly reduces the risk of ischemic heart disease, but the adherence of long-term statin use is far from satisfactory. In addition, a previous study shows that "more than 90% of patients with statin-associated muscle symptoms can keep on taking statins over the long term and gain the full clinical benefit of statin treatment after a switch to another type of statin or a readjustment of the dose or frequency of administration" (Laufs et al, 2015). That's why our analysis only included participants with long-term statin therapy.

We agree with you, the inclusion criteria of this analysis might miss people who stopped taking statins prior the study or stopped at the early use of statin due to side-effect. We have added this point as a limitation. (Page 14 paragraph 3)

6. How did the doses differ between the two groups and was there any evidence of better adherence with Vitamin D in those on higher doses? Also, it would be interesting to convert statin dose into "atorvastatin units" and then to compare adherence etc between groups on similar doses of statin and similar duration of treatment. This would require calculating an "atorvastatin does equivalent x days of treatment" metric.

RESPONSE: Thank you for your suggestions. We have done further analyses at your suggestion and found that the average atorvastatin equivalent dose over the 24 month period was similar in the two treatment groups (vitamin D group 23.7 (19.2) mg vs. placebo 23.1 (17.7) mg, p=0.12); and that the total amount of atorvastatin dose equivalent (atorvastatin daily dose * days of supply) also was similar in the vitamin D group (mean=14,906, SD=13,123 mg) compared to the placebo group (mean=14,247, SD=13,123 mg) over a 24-month follow-up, but there was no significant difference (p=0.19) (Results Page 11). In addition, we have added a subgroup analysis among these participants with high atorvastatin equivalent dose (≥40 mg/day). We did not find a significant difference in the adherence of statin between two groups (RR=1.01, p=0.74) (Results Page 11).

7. Did the 90 days of statin use start after randomization so people who came in on statins would not have qualified for 90 days?

RESPONSE: All the participants in this studies would require at least 90 days statin therapy in the study period. The measurement period of this study began on the ***index date*** (the first day with statin therapy after the date of randomization) and extended for a subsequent fixed period (e.g. 6-, 12-, 24-month) or until death (see Method Page 7 paragraph 2 & Supplementary Figure 1).

8. On page 12, the authors state that simvastatin was the most popular statin, but more people were on atorvastatin. This is not clear.

RESPONSE: We have revised the text to "first-line statin". (Pages 2 &11)

9. Page 12, line 52-57: It is unclear why changing the statin decreased persistence. Is this calculated per person or per drug? If the person continues but on a different statin that should not count against the patient being persistent.

RESPONSE: We agree with you. In the calculating of persistence of all statins, if the person continues but on a different statin, we did not count against the patient being persistent. However, for the persistence with specific statin (e.g. simvastatin only), if the person continues but on a different statin (e.g. atorvastatin), we did count against the patient being persistent. The later situation occurred in very few participants. As stated in the results, most statin users (87%) were dispensed one category of statin during the study period. (Page 10, last paragraph).

10. Figure 2, the statement "The persistence calculation in the baseline measurement (6 months before randomization) only for participants on statin therapy during that period." Is not clear to this reviewer. The role of pre study statin adherence/persistence needs to be discussed in the text.

RESPONSE: Thank you for your comments, we have revised the explanation of this sentence (Page 10 paragraph 2) – "During the baseline measurement period (6 months before randomization), some participants (15.8%) selected for this analysis were not on prescribed statins because they started after randomization. Regardless, adherence during the 6 months prior to randomization to taking all statins and individual statins was similar between vitamin D and placebo groups …".
The legend of Figure 2 has been revised. The related discussion have been added in Page 14, paragraphs 2 & 3.

References

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Editorial Office comments:

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- Make sure to apply the formatting requirements to all figures and tables where necessary (e.g. style of p values, gene and protein nomenclature).
- Make sure to use uniform lettering and sizing of your original artwork, including letters to indicate panels, throughout all figures.
- Make sure to submit high resolution versions of each figure.

RESPONSE: Thank you for your comments, we have revised our manuscripts.

*Statement of Originality

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06 December 2017

Editor,
Atherosclerosis

Dear Editor,

We are submitting a manuscript titled:

Effects of vitamin D supplementation on adherence and persistence with long-term statin therapy in older adults

I confirm that the results in this manuscript have not been published previously, nor are they being considered for publication by another journal.

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06 December 2017

Editor,
Atherosclerosis

Dear Editor,

We are submitting a manuscript titled:

Effects of vitamin D supplementation on adherence and persistence with long-term statin therapy in older adults

To our knowledge, no randomized controlled trials have explored whether vitamin D supplementation can improve the adherence and persistence with taking statins. All participants on long-term statin therapy in a population-based trial of vitamin D supplementation were selected to assess the effects of vitamin D supplementation on long-term adherence and persistence with taking statins.

Our results show that monthly vitamin D supplementation improved persistence with taking statins over a 24-month measurement period in older adults on long-term statin therapy. We believe that this finding maybe of clinical significance to the readers of your Journal. We would like to submit this to the original contribution section of your Journal.

These results have not been published previously, nor are they being considered for publication by another journal.

The authors (in order of authorship) are: Zhenqiang Wu, MSc; Carlos A. Camargo Jr, MD, DrPH; Kay-Tee Khaw, MBBChir, MSc, Debbie Waayer, MEd; Carlene M.M. Lawes, MBChB, PhD; Les Toop, MBChB, MD; Robert Scragg, MBBS, PhD

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Yours sincerely,

Robert Scragg, MBBS, PhD

Professor of Epidemiology
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***Conflict of interest form**

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Figure 1

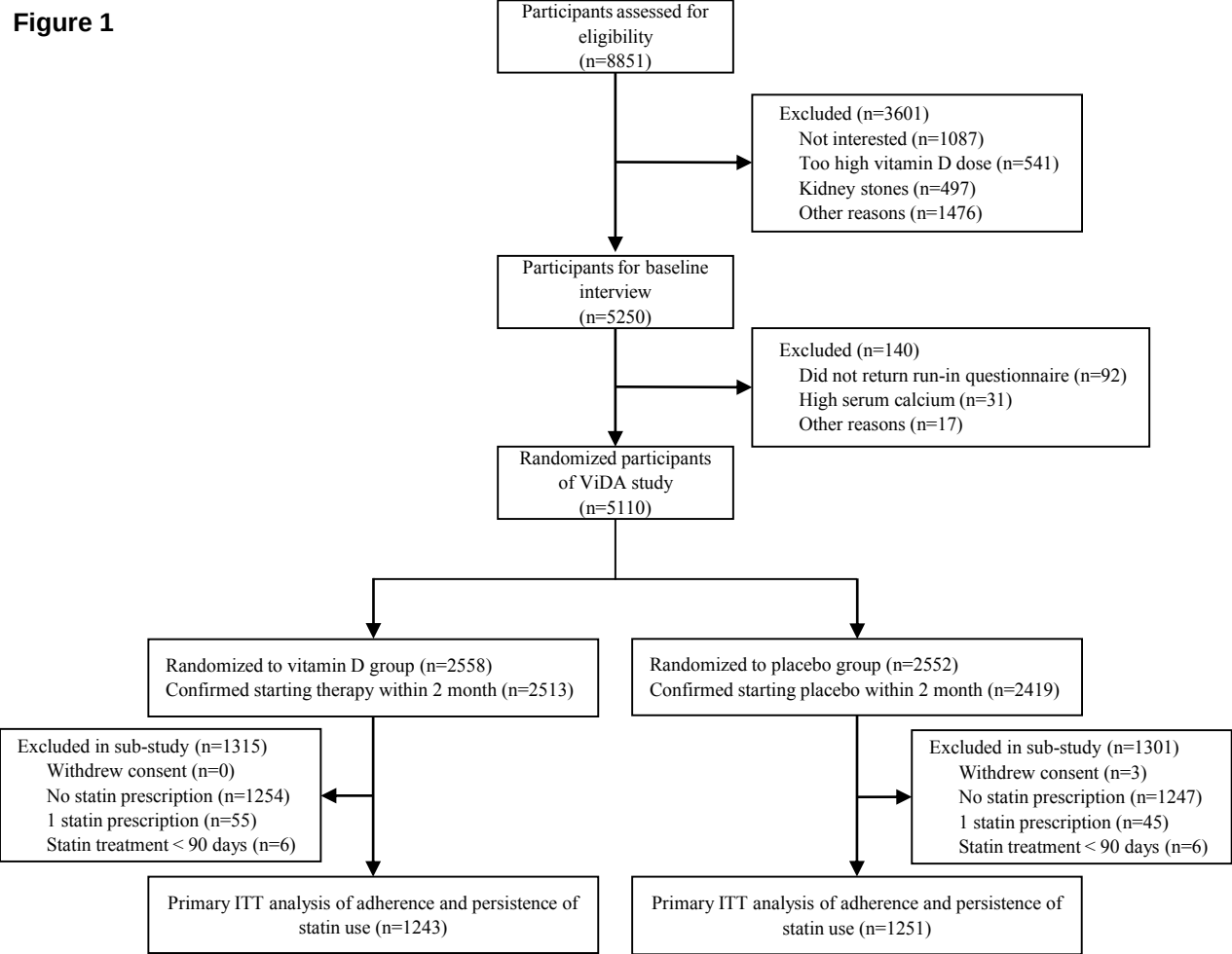
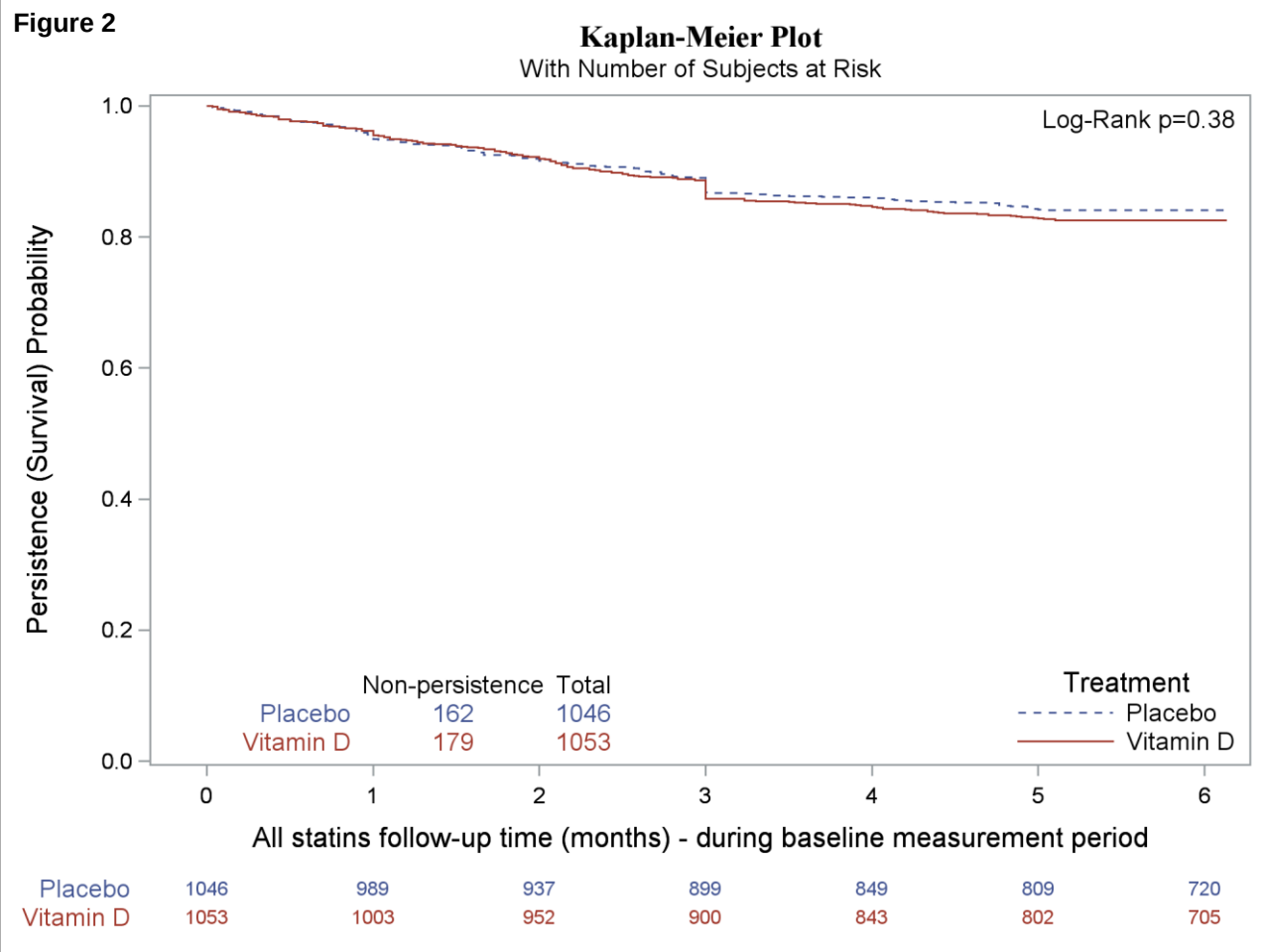
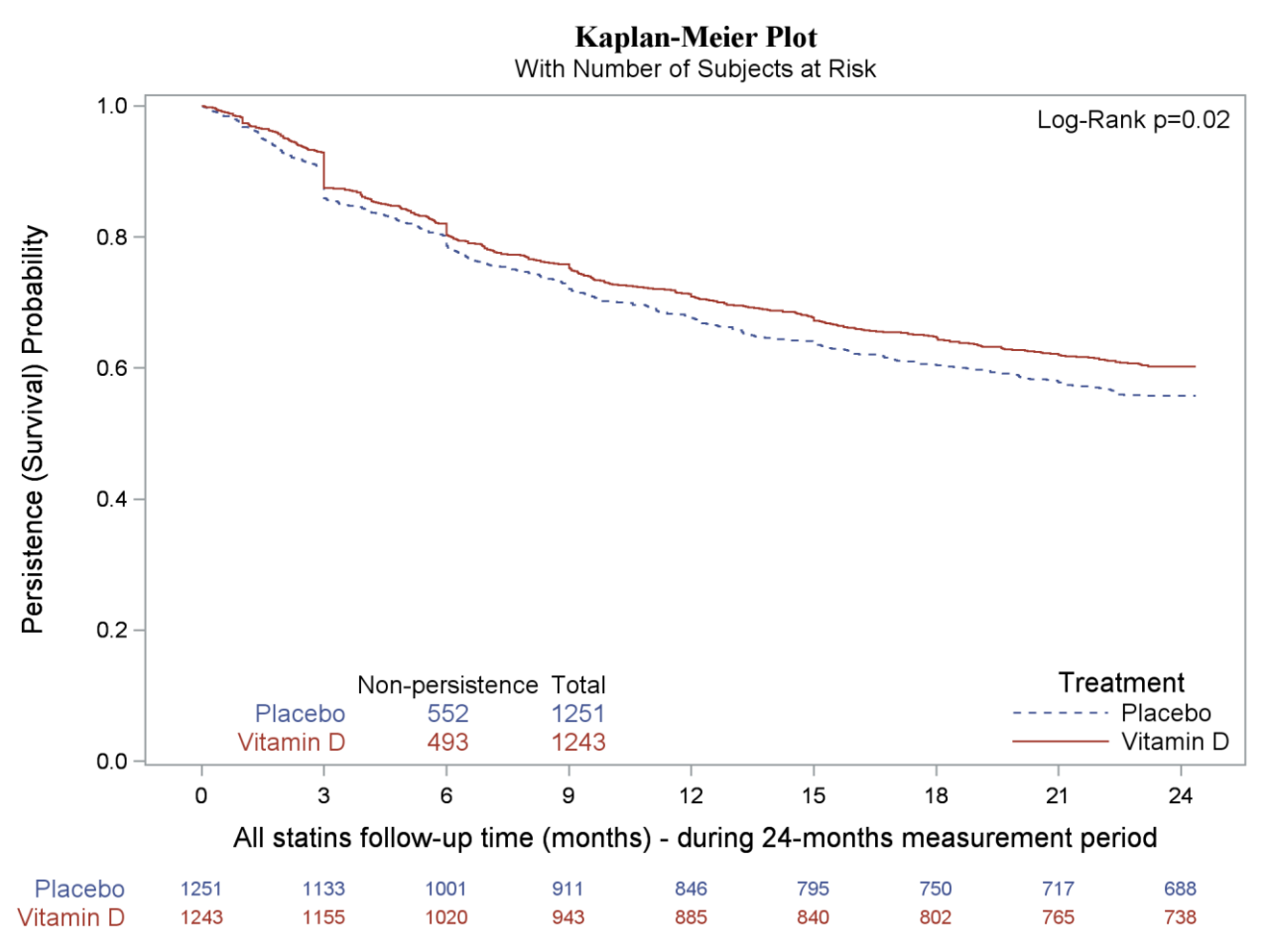

Participants assessed for eligibility (n=8851)
Excluded (n=3601)
Not interested (n=1087)
Too high vitamin D dose (n=541)
Kidney stones (n=497)
Other reasons (n=1476)
Participants for baseline interview (n=5250)
Excluded (n=140)
Did not return run-in questionnaire (n=92)
High serum calcium (n=31)
Other reasons (n=17)
Randomized participants of ViDA study (n=5110)
Randomized to vitamin D group (n=2558)
Confirmed starting therapy within 2 month (n=2513)
Randomized to placebo group (n=2552)
Confirmed starting placebo within 2 month (n=2419)
Excluded in sub-study (n=1315)
Withdrew consent (n=0)
No statin prescription (n=1254)
1 statin prescription (n=55)
Statin treatment < 90 days (n=6)
Excluded in sub-study (n=1301)
Withdrew consent (n=3)
No statin prescription (n=1247)
1 statin prescription (n=45)
Statin treatment < 90 days (n=6)
Primary ITT analysis of adherence and persistence of statin use (n=1243)
Primary ITT analysis of adherence and persistence of statin use (n=1251)

Figure 2


Kaplan-Meier Plot
With Number of Subjects at Risk
Log-Rank p=0.38
Persistence (Survival) Probability
1.0
0.8
0.6
0.4
0.2
0.0
Non-persistence Total
Placebo 162 1046
Vitamin D 179 1053
Treatment
Placebo
Vitamin D
0 1 2 3 4 5 6
All statins follow-up time (months) - during baseline measurement period
Placebo 1046 989 937 899 849 809 720
Vitamin D 1053 1003 952 900 843 802 705


Kaplan-Meier Plot
With Number of Subjects at Risk
Log-Rank p=0.02
Persistence (Survival) Probability
1.0
0.8
0.6
0.4
0.2
0.0
Non-persistence Total
Placebo 552 1251
Vitamin D 493 1243
Treatment
Placebo
Vitamin D
0 3 6 9 12 15 18 21 24
All statins follow-up time (months) - during 24-months measurement period
Placebo 1251 1133 1001 911 846 795 750 717 688
Vitamin D 1243 1155 1020 943 885 840 802 765 738

Supplementary Material for online publication only

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- Abstract in the Atherosclerosis format (*Background and aims*, *Methods*, *Results*, *Conclusions*)
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Conflict of interest (mandatory)
- Financial support (if applicable)
- Author contributions (mandatory)
- Acknowledgements (if applicable)
- References
- Figures and Tables (with legends in the suitable style)

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Is the Abstract structured in the below sections? **Yes**

- *Background and aims*
- *Methods*
- *Results*
- *Conclusions*

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Are figure and table legends formatted as described below? **Yes**

Each figure and table legend should have a brief overarching title that describes the entire figure without citing specific panels, followed by a description of each panel, and all symbols used.

If a figure or table contains multiple panels, the letter describing each panel should be capitalized and surrounded by parenthesis: i.e. (A)(B)(C)(D).

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Footnotes to tables should be listed with superscript lowercase letters, beginning with "[a]."
Footnotes must not be listed with numbers or symbols.

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Are abbreviations defined when first used in the text? **Yes**

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Are units expressed following the international system of units (SI)? **Yes**

If other units are mentioned, please provide conversion factors into SI units.

DNA and protein sequences

Are gene names italicized? **NA**

Gene names should be italicized; protein products of the loci are not italicized.

For murine models, the gene and protein names are lowercase except for the first letter.
(e.g., gene: *Abcb4;* protein: Abcb4)

For humans, the whole gene name is capitalized.
(e.g., gene: *ABCB4;* protein ABCB4)

Mouse strains and cell lines

Are knock-out or transgenic mouse strains and cell lines italicized and the symbol superscripted? NA

(e.g. *ob/ob* , $p53^{+/+}$, $p53^{-/-}$)

p values

Are *p* values consistently formatted according to the below style throughout the manuscript (including figures and tables)? **Yes**

p <X
p >X
p=X

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Is your manuscript written in good English? **Yes**

Please make sure that you consistently use either American or British English, but not a mixture of them.

Please make sure that words are written consistently in the same way throughout the manuscript.
e.g. non-significant or nonsignificant
e.g. down-regulation or downregulation

Artwork

Have you submitted high-resolution versions of your original artwork? **Yes**

Please make sure to use uniform lettering and sizing in your original artwork, including letters to indicate panels, consistently throughout all figures.